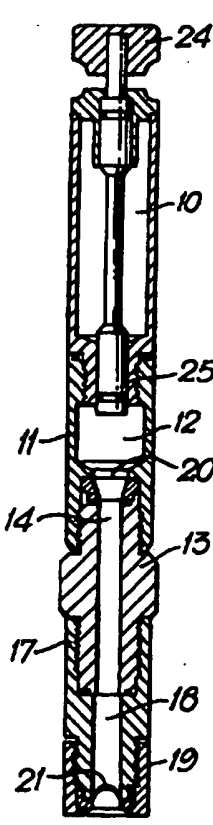


PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61M 5/30, 25/00	A1	(11) International Publication Number: WO 96/20022 (43) International Publication Date: 4 July 1996 (04.07.96)
(21) International Application Number: PCT/GB95/03016 (22) International Filing Date: 21 December 1995 (21.12.95) (30) Priority Data: 9426379.5 23 December 1994 (23.12.94) GB (71) Applicant (for all designated States except US): OXFORD BIOSCIENCES LIMITED [GB/GB]; The Magdalen Centre, The Oxford Science Park, Oxford OX4 4GA (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BELLHOUSE, Brian, John [GB/GB]; The Lodge, North Street, Islip, Oxfordshire OX5 2SQ (GB). BELL, John [CA/GB]; The Dairy, Lower Street, Islip OX5 5SG (GB). (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: PARTICLE DELIVERY (57) Abstract <p>A needleless syringe comprising a body containing a lumen, an upstream end of which is, or is arranged to be, connected to a source of gaseous pressure which can suddenly be released into the lumen; the downstream end of the lumen terminating behind a bistable diaphragm which is movable between an inverted position in which it presents outwardly of the body a concavity for containing particles of a therapeutic agent, and an everted, outwardly convex, position; the arrangement being such that, in use, when gas under pressure is released into the lumen, the diaphragm will snap over from its inverted to its everted position and catapult the particles outwardly.</p> 		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PARTICLE DELIVERY

In our earlier WO94/24263, we disclose a non-invasive drug delivery system involving the use of a needleless syringe which fires particles of a therapeutic agent in controlled doses into body tissue, e.g. through the intact skin, or delivers genetic material into living cells. The syringe described in the earlier application is constructed as an elongate tubular nozzle, a rupturable membrane initially closing the passage through the nozzle adjacent to the upstream end of the nozzle, particles of a therapeutic agent located adjacent to the membrane, and energising means for applying to the upstream side of the membrane a gaseous pressure sufficient to burst the membrane and produce through the nozzle a supersonic gas flow in which the particles are entrained.

As explained in the earlier specification, the particles of the therapeutic agent may be carrier particles coated, for example, with genetic material, or may be powdered drugs for all kinds of therapeutic use. Similarly the earlier specification explains the parameters of particle size (preferably 10-40 μm) density (preferably 0.5-2.0 g/cm^3), and velocity (preferably 200-2500 m/sec), and momentum density (preferably 4-7 kg/sec/m), which have been found to be appropriate for adequate target penetration. These parameters are unchanged but we have now devised a modification of the particle delivery system.

According to the present invention, a needleless syringe comprises a body containing a lumen, an upstream end of which is, or is arranged to be, connected to a source of gaseous pressure which can suddenly be released into the lumen; the downstream end of the lumen terminating behind a bistable diaphragm which is movable between an inverted position in which it presents outwardly of the body a concavity for containing particles of a therapeutic agent, and an everted, outwardly convex, position; the arrangement being such that, in use, when gas under

pressure is released into the lumen, the diaphragm will snap over from its inverted to its everted position and catapult the particles outwardly.

5 This new construction has an advantage that even when, as will be usual, a gaseous supersonic shockwave will be necessary to snap the diaphragm over from its inverted to its everted position, the diaphragm will contain the gas within the lumen so that no provision has to be made for dissipating and silencing any shockwave reflected from the
10 target. Also the target tissue is not subjected to any possibility of harm from the high speed gas flow.

As disclosed in the earlier specification, the release of the pressurized gas may be achieved by building up pressure behind a rupturable membrane until the pressure
15 difference across the membrane is sufficient to rupture the membrane and release the gas suddenly into the lumen. Alternatively the syringe may incorporate a reservoir of compressed gas having a valve which can be opened suddenly to release the gas into the lumen. In both cases, the
20 velocity of the shockwave is increased if the gas is lighter than air, e.g. helium. This effect is enhanced if the lumen is also initially filled with a gas, which is lighter than air, e.g. helium.

In order to avoid loss of particles prior to delivery
25 and to maintain sterility of the particles, the concavity is preferably covered by, for example, a retractable shield or a thin barrier film which is readily penetrated by the particles upon ejection.

The syringe may be constructed for the transdermal
30 delivery of drugs into the body, in which case the lumen may be provided by the passageway through a tubular nozzle, the diaphragm being provided adjacent to the downstream end of the nozzle and facing substantially in the axial direction of the nozzle. Alternatively, the invention may
35 be used in conjunction with a catheter, such as an arterial catheter, in which case the diaphragm may be provided in a sidewall of the catheter body so that upon eversion, the

particles are propelled laterally from the body. This would find use in vascular proliferative diseases for delivering genetic material into the wall of the expanded stenotic blood vessel, to transform genetically the endothelial cells lining the wall of the blood vessel with the aim of preventing subsequent restenosis/re-occlusion of the blood vessel.

Moreover, the development of a catheter-based delivery system may find other uses, as for localised delivery of a combination of compounds (eg for chemotherapy) into specific internal organs and for the local organ-based hormone replacement. The catheter device would also be useful in the administration of drugs or DNA to accessible surfaces for medical purposes (eg for the treatment of tumours of mucosal surfaces, such as respiratory, gastrointestinal or genito-urinary tracts).

The invention is illustrated by way of example in the accompanying drawings.

Figures 1 to 3 show a syringe for transdermal delivery of particles of therapeutic agent. Thus as particularly shown in Figure 1 the syringe has a cylindrical reservoir 10 initially containing helium under a pressure of about 80 bar. This is screwed and sealed to a first tubular body portion 11 containing a rupture chamber 12. The body portion 11 is screwed and sealed to a second tubular body portion 13 containing a passageway 14. In turn the body portion 13 is screwed and sealed to a third tubular body portion 17 containing a passageway 18, and a tubular tip portion 19 is screwed to the bottom of the body portion 17.

With this construction the reservoir 10 can be stored separately and fitted to the rest of the syringe immediately prior to use. The body portions 11 and 13 are separable to allow the sandwiching between them of a rupturable membrane 20. The tip portion 19 is separable from the body portion 17 to allow the sandwiching between them of an invertible bistable diaphragm 21 which is shaped in the form of a dome from a stiff and strong, but

resilient, material such as Mylar by thermoforming in a suitable jig. The body portions 13 and 17 are separable so that the parts 17, 19 and 21 can be provided as a disposable unit.

5 Particles of therapeutic agent will initially be provided in the concavity at the externally facing surface of the diaphragm 21. The particles may be attached by electrostatic forces, by their natural sticky nature, or by the evaporation of ethanol in which the particles have been
10 suspended. Preferably, however, and for reasons of sterility, the diaphragm 21 is covered and sealed at its edge to a weak barrier film 22 to form a sealed capsule containing the particles 23, as shown in Figure 3. The weak barrier film 22 may be cut or scored to assist rupture
15 and reduce membrane fragmentation.

 In use with the syringe assembled and with the lumen 14, 18 prefilled with helium at approximately atmospheric pressure, the tip is placed in proximity to, or in contact with, the skin to be treated and a plunger 24 is depressed
20 to open a valve 25 and allow the helium to be discharged into the rupture chamber 12. This valve 25 may preferably be arranged such that the frontal area of the plunger is greater at the downstream exit to the cylindrical reservoir 10 when compared with the upstream frontal area of the
25 plunger, resulting in a self-opening (and quick-opening) valve. When the pressure in the chamber 12 has reached a sufficient value of, for example, about 23 bar, the membrane 20 bursts, releasing a shockwave which propagates through a lumen, i.e. a nozzle, formed by the passageways
30 14 and 18, and causes the diaphragm 21 suddenly to evert into a downwardly, outwardly convex, configuration. This propels the particles 23 rapidly forward out of the syringe with simultaneous rupture of the barrier film 22.

 As suggested in Figure 3, a short tubular spacer 26
35 may be provided to reduce the velocity of the particles before impact and to enable the particles to become more spread out in order to increase the target area of skin.

Figures 4 to 7 show the application of the invention to an arterial catheter for use in vascular proliferative disorders.

Figure 5 shows the whole catheter, provided at its upstream end with a reservoir 10, valve 25, rupture chamber 12 and rupturable membrane 20, similar to those of the first example. The catheter may be a triple lumen catheter, one lumen for the usual guidewire, the second to carry gas to inflate a positional balloon 27 for urging a body 28 adjacent to the leading end (shown in Figure 4) of the catheter against a wall of an artery 29, and the third 30 for propagating a shockwave to the tip of the catheter.

At an opening 31 in a sidewall of the catheter body 28, there is provided a bistable diaphragm 32. In a position shown in Figure 4 and in full lines in Figure 6, the diaphragm presents a laterally outwardly facing concavity in which particles of therapeutic agent, such as particles 33, e.g. containing or consisting of DNA, are located. In order to avoid the particles being washed out of the concavity by means of the blood flow in the artery the cavity may initially be covered by a barrier film or by a retractable sleeve 35 as shown in Figure 7.

The catheter is used analogously to the syringe of Figures 1 to 3. Thus release of helium from the reservoir 10 into the rupture chamber 12 eventually bursts the membrane 20 and causes a shockwave to be propagated along the lumen 30 causing the diaphragm 32 to evert suddenly to the dotted line position shown in Figure 6 and hence to propel the particles 33 outwardly, after retraction of the sleeve 35 or through the barrier film, into the wall of the artery 29.

Contrary to what is shown in Figure 6, it may be desirable for the diaphragm 32 to be within the peripheral envelope of the catheter body, not only when in its inverted position in order to avoid interference during insertion of the catheter, but also when in its everted

position to avoid potentially damaging impact with the arterial wall.

CLAIMS

1. A needleless syringe comprising a body (13,17;28) containing a lumen (14,18;30), an upstream end of which is, or is arranged to be, connected to a source (10) of gaseous pressure which can suddenly be released into the lumen; the downstream end of the lumen terminating behind a bistable diaphragm (21,32) which is movable between an inverted position in which it presents outwardly of the body a concavity for containing particles (23,33) of a therapeutic agent, and an everted, outwardly convex, position; the arrangement being such that, in use, when gas under pressure is released into the lumen, the diaphragm will snap over from its inverted to its everted position and catapult the particles outwardly.

2. A syringe according to claim 1, wherein the upstream end of the lumen (14,18;30) is initially closed by a rupturable membrane (20) which, when subjected to gas under sufficient pressure is arranged to rupture and release the gas suddenly into the lumen.

3. A syringe according to claim 1 or claim 2, in which the lumen (14,18;30) initially contains a gas which is lighter than air.

4. A syringe according to any one of the preceding claims, in which particles (23,33) of a therapeutic agent are located in the concavity of the inverted diaphragm.

5. A syringe according to claim 4, in which the particles in the concavity are covered by a retractable shield (35).

6. A syringe according to claim 4, in which the particles in the cavity are covered by a thin barrier film (22) which is readily penetrated by the particles upon ejection.

7. A syringe according to any one of the preceding claims, in which the lumen-containing body is a tubular nozzle (14,18), the diaphragm (21) being provided adjacent to the downstream end of the nozzle and facing substantially in the axial direction of the nozzle.

8. A syringe according to claim 7, in which a tubular spacer (26) projects from the nozzle downstream of the diaphragm.
9. A syringe according to any one of claims 1 to 6, in
5 which the lumen-containing body is a catheter (28).
10. A syringe according to claim 9, in which the diaphragm (32) is provided in a side wall of the catheter body so that, upon eversion of the diaphragm, the particles (33) are propelled laterally from the body.
- 10 11. A product for therapeutic use, the product comprising a unit of or for a syringe according to any one of the preceding claims, the unit comprising a dome-shaped diaphragm in the concave side of which are sealed particles of a therapeutic agent, the diaphragm being arranged
15 suddenly to evert under a gaseous shock-wave applied to the convex side of the dome whereby the particles are catapulted outwardly from the diaphragm.
12. A product according to claim 1, wherein the particles are sealed between the concave side of the diaphragm and a
20 covering barrier film which is sealed to the diaphragm.
13. A method of therapeutic treatment by the injection of particles of therapeutic agent into bodily tissue, the method comprising providing the particles in the concave side of a dome-shaped diaphragm, and applying a gaseous
25 shockwave to the convex side of the dome whereby the dome suddenly everts and catapults the particles outwardly from the diaphragm.

1/2

Fig.1.

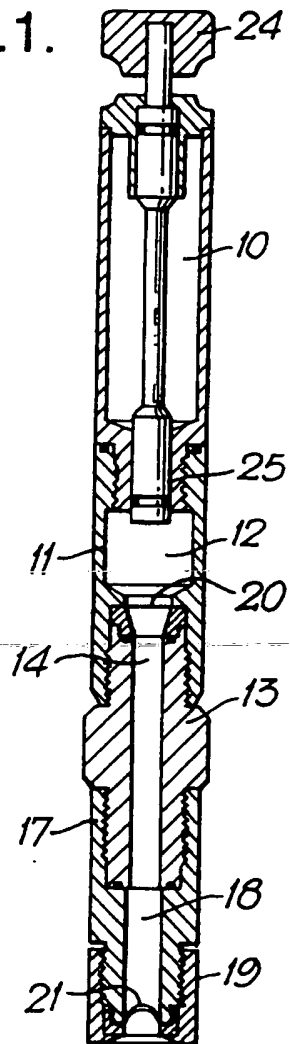


Fig.2.

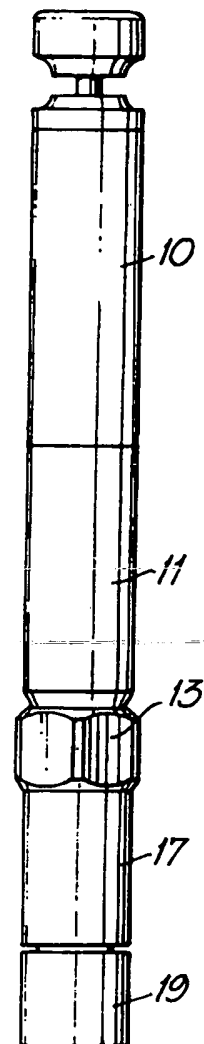
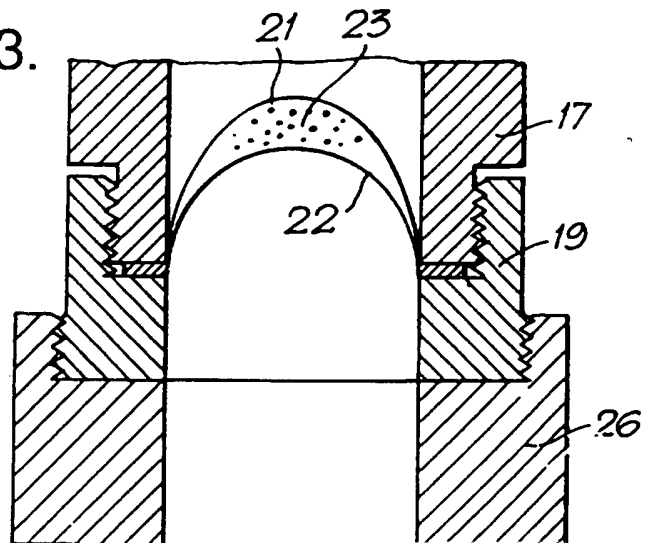


Fig.3.



2/2

Fig.4.

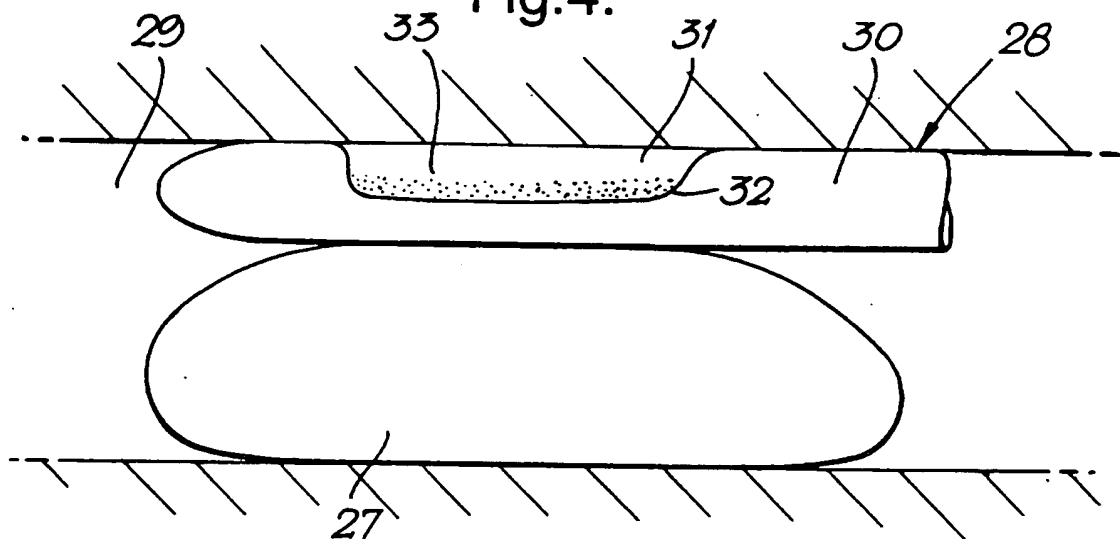


Fig.5.

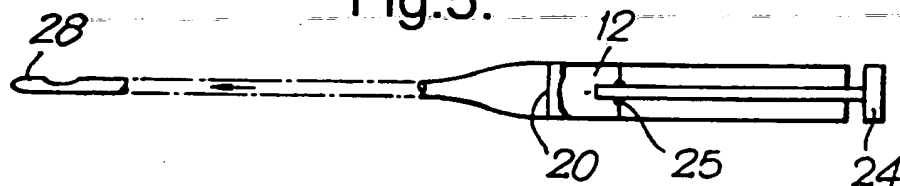


Fig.6.

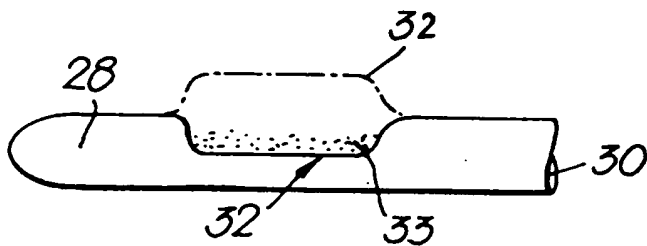
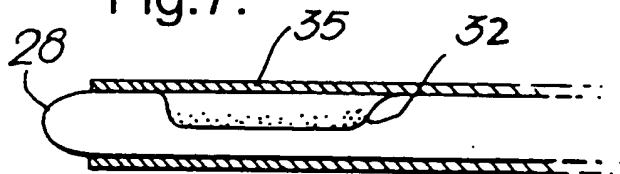


Fig.7.



INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/03016

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M5/30 A61M25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M C12M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,3 308 818 (RUTKOWSKI) 14 March 1967 see column 1, line 11 - column 2, line 31 see figures 1,1A,1B	1
Y	--- EP,A,0 370 571 (HOLZER) 30 May 1990 see column 3, line 27 - column 4, line 37 see figures 1-7	1,4,5,7, 11
Y	--- US,A,4 945 050 (SANFORD ET AL.) 31 July 1990 see column 8, line 52 - line 66 see figures 8A,8B --- -/--	1,4,5,7, 11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

11 April 1996

Date of mailing of the international search report

17. 04. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (- 31-70) 340-3016

Authorized officer

Schönleben, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 95/03016

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 24263 (OXFORD BIOSCIENCES LIMITED) 27 October 1994 cited in the application see page 16, line 26 - page 19, line 24 see figure 1 ---	2,3,8
A	US,A,5 282 785 (SHAPLAND ET AL.) 1 February 1994 see column 4, line 3 - line 61 see figures 1,2 ---	9,10
A	EP,A,0 469 814 (LILLY INDUSTRIES LIMITED) 5 February 1992 see column 3, line 30 - column 4, line 33 see figures 5,6,11,12 ---	11,12
A	GB,A,2 206 794 (POWER ET AL.) 18 January 1989 see page 2, line 15 - line 36 see figures 1,2 -----	11,12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/03016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3308818	14-03-67	NONE	
EP-A-370571	30-05-90	DE-A- 3839287	23-05-90
		DE-A- 3901691	26-07-90
		DE-D- 58905835	11-11-93
		JP-A- 2232060	14-09-90
		US-A- 5026343	25-06-91
US-A-4945050	31-07-90	US-A- 5478744	26-12-95
		US-A- 5100792	31-03-92
		US-A- 5036006	30-07-91
		US-A- 5371015	06-12-94
WO-A-9424263	27-10-94	AU-B- 6435194	08-11-94
		BR-A- 9406455	02-01-96
		CA-A- 2159452	27-10-94
		EP-A- 0693119	24-01-96
		FI-A- 954788	06-10-95
		NO-A- 953994	06-10-95
		PL-A- 311005	22-01-96
		ZA-A- 9402442	10-04-95
US-A-5282785	01-02-94	US-A- 5286254	15-02-94
		AT-T- 123658	15-06-95
		AU-B- 8074591	07-01-92
		DE-D- 69110467	20-07-95
		DE-T- 69110467	01-02-96
		EP-A- 0533816	31-03-93
		WO-A- 9119529	26-12-91
		US-A- 5498238	12-03-96
		US-A- 5499971	19-03-96
		US-A- 5458568	17-10-95
		AU-B- 3321293	29-03-94
		AU-B- 3321793	29-03-94
		EP-A- 0611311	24-08-94
		JP-T- 7500523	19-01-95
		WO-A- 9405361	17-03-94
		WO-A- 9405369	17-03-94
EP-A-469814	05-02-92	CA-A- 2047823	01-02-92

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/03016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-469814		JP-A- 5123399	21-05-93
GB-A-2206794	18-01-89	NONE	